Editorial

Amiodarone in congestive heart failure: unravelling the GESICA and CHF-STAT differences

Patients with congestive heart failure are at an increased risk of sudden death. Heart failure is the most common cardiovascular discharge diagnosis in elderly patients in the United States, and its incidence more than doubles each decade after the age of 45. The aging population will further increase the number of patients in whom congestive heart failure is diagnosed. Two recent studies have evaluated the role of amiodarone in improving survival in patients with congestive heart failure. The Survival Trial Of Antiarrhythmic Therapy In Congestive Heart Failure (CHF-STAT)[1] was performed in Veterans' Administration hospitals in the United States, and the Gruppo de Estudo de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA) was performed in Argentina.[2] Unfortunately, the studies had divergent results, making clear recommendations difficult.

Arrhythmia in patients with congestive heart failure
Recent studies using angiotensin converting enzyme (ACE) inhibitors have demonstrated significantly increased survival in patients with moderately symptomatic congestive heart failure. In the SOLVED and V-HeFT II trials, the 2·5 year mortality in patients treated with ACE inhibitors was 25–27% with 23% of patients in SOLVED dying an arrhythmic death without worsening congestive heart failure, and 57% of patients in V-HeFT II dying suddenly with or without warning symptoms. Thus about 25–50% of deaths in patients with congestive heart failure are related to arrhythmia (both tachyarrhythmia and bradyarrhythmia). Amiodarone was chosen in GESICA and CHF-STAT because of its low risk of proarrhythmia[3] and of worsening heart failure in patients with already reduced ventricular function. Previous studies of amiodarone in patients with cardiomyopathy, ventricular arrhythmias, and congestive heart failure have reported inconsistent results: Neri *et al*[4] reported an improved survival, Cleland *et al*[5] reported a decreased incidence of sudden death, and Nicklas *et al*[6] reported no improvement.

GESICA
This trial openly randomised 516 patients optimally treated for congestive heart failure to receive either amiodarone (600 mg daily for 14 days followed by 300 mg

daily) or no additional treatment. The mean aged was 59 years and 80% were male. Eighty per cent of patients had class III or IV heart failure with associated myocardial infarction in 40%, idiopathic dilated cardiomyopathy in 20%, alcoholism in 30%, and Chagas' disease in 10%. Patients with angina were excluded. Mean follow up was 13 months with 33·5% deaths in the amiodarone group and 41·4% deaths in the control group for a risk reduction of 28% (P = 0·024). In the amiodarone group, there was a 27% (P = 0·16) reduction in sudden death, a 23% (P = 0·16) reduction in progressive congestive heart failure, and a 31% (P = 0·002) reduction in hospital admissions for worsening congestive heart failure. The reduction in mortality and hospital admission was present in subgroup analysis for gender, heart failure class, and presence or absence of nonsustained ventricular tachycardia. Two year survival in the amiodarone group was approximately 60% compared with 45% in the control group. Five per cent of patients stopped amiodarone because of side effects (0·35% per month of follow up). The authors concluded that low dose amiodarone was an effective and reliable treatment that reduced both mortality and hospital admissions in patients with severe congestive heart failure, and these benefits were independent of the presence of complex ventricular arrhythmias.

CHF-STAT
This recently published trial blindly randomised 674 patients optimally treated for congestive heart failure to receive either amiodarone (800 mg daily for 14 days, then 400 mg daily for 50 weeks, then 300 mg daily) or placebo in addition to their conventional treatment. The mean age was 65 years and 99% were male. Forty two per cent of patients had class III or IV heart failure which was due to coronary artery disease in 72% and dilated cardiomyopathy in 28%. Mean follow up was 45 months with no significant survival difference between the two treatment groups (P = 0·6). The 2 year actuarial survival rate was 69·4% for patients in the amiodarone group and 70·8% for patients in the placebo group. There was a trend toward a reduction in overall mortality among patients with non-ischaemic cardiomyopathy who received amiodarone (P = 0·07). Amiodarone did improve left ventricular ejection fraction by 42% at 2 years. Twenty seven per cent of patients stopped amiodarone because of side effects (0·6% per month of follow up). This trial showed that amiodarone was effective in suppressing ventricular arrhythmias and improving ventricular function but did not reduce the incidence of sudden death or prolong survival in patients with congestive heart failure. There was a trend toward reduced mortality among patients with a non-ischaemic cardiomyopathy.

Why did the two trials reach different conclusions?
There is no clear and easy explanation for the different results in the two trials. GESICA supports the routine use

Glossary	
CHF-STAT	= survival trial of antiarrhythmic therapy in congestive heart failure
GESICA	= gruppo de estudio de la sobrevida en la insuficiencia cardiaca en Argentina
SOLVED	= studies of left ventricular dysfunction
V-HeFT	= Veterans heart failure trial
CAMIAT	= Canadian amiodarone myocardial infarction arrhythmia trial
CASCADE	= conventional versus amiodarone drug evaluation trial
BASIS	= basal antiarrhythmic study of infarct survival

of amiodarone in patients with congestive heart failure while CHF-STAT does not. Differences between the two trials include the patient's age, the predominance of men in CHF-STAT, severity of heart failure, adherence to treatment, and difference in underlying heart disease.

CHF-STAT patients were approximately 6 years older which should have had no important influence on the outcome. Ninety nine per cent of CHF-STAT patients were male compared with 79% of GESICA patients. Increased body surface area in males may have decreased the relative efficacy of amiodarone (both studies used a maintenance dose of 300 mg a day). However, this should have less effect because of the increased dosing regimen for CHF-STAT which resulted in a first-year cumulative dose of amiodarone that was 33% higher. Other studies of amiodarone have not reported a difference in efficacy based on gender.[7 8] The GESICA patients had more advanced congestive heart failure with nearly 80% in class III or IV compared with 42% in CHF-STAT. In addition, 2 year mortality in the control group of GESICA was 55% compared with 30% in CHF-STAT. It is possible that patients who have advanced heart failure with an increased risk of mortality will show a more striking benefit from a medicine that is only marginally effective in a healthier population. This argument is less persuasive in the context of the BASIS trial[7] where amiodarone efficacy in patients after myocardial infarction was only significant in those with an ejection fraction greater than 40%.

More patients in CHF-STAT than in GESICA stopped taking amiodarone because of side effects. The 27% of patients who stopped amiodarone during the mean follow up of 45 months resembles other studies such as CASCADE[9] where 25% of patients stopped amiodarone at 2 years, and the CAMIAT[10] pilot study where 35% of patients discontinued amiodarone at 20 months. This rate of drug discontinuation should not have accounted for the divergent results in the studies.

The most striking difference between the two studies is the nature of the underlying heart disease. In CHF-STAT, 72% of patients had ischaemic cardiomyopathy compared with only 40% of patients with a history of myocardial infarction in GESICA. Patients with any angina within 3 months of entry were excluded. The remaining patients in GESICA had either idiopathic cardiomyopathy or cardiomyopathy secondary to alcoholism or Chagas' disease. Although previous studies[7 8] showed that amiodarone is effective in preventing subsequent death in patients after acute myocardial infarction, BASIS,[7] as previously mentioned, showed that this effect was not present in patients with ejection fraction <40%. Patients in CHF-STAT with ischaemic cardiomyopathy may have had a similar lack of benefit from amiodarone. Such patients may also be liable to bradyarrhythmias related to advancing ischaemia which would be aggravated by amiodarone, resulting in death from bradycardia. The 30% of patients who were alcoholic and 10% who had Chagas' disease in GESICA may be patients who show a unique response to amiodarone. CHF-STAT did show a trend toward mortality reduction among patients with non-ischaemic cardiomyopathy who received amiodarone, a finding similar to GESICA.

Sudden cardiac death in heart failure: trial of prophylactic amiodarone versus implantable defibrillator therapy (SCD-HeFT)

SCD-HeFT was prompted by the failure of previous trials to come to consistent and helpful conclusions. This trial

compares conventional treatment alone versus addition of amiodarone versus addition of a pectorally implanted third generation implantable cardioverter defibrillator in 2500 patients with an ejection fraction ≤35%, class II or III congestive heart failure, and idiopathic or ischaemic cardiomyopathy. The addition of a defibrillator capable of bradycardia pacing will presumably prevent death from both tachyarrhythmia and bradyarrhythmia. The pilot study enrolment has been completed. This study will be put in context with GESICA and CHF-STAT to help define optimal treatment to prevent arrhythmic deaths in patients with congestive heart failure.

Clinical implications and recommendations

Clear enthusiastic recommendations concerning the approach to prevention of arrhythmic death in patients with congestive heart failure cannot come from these two conflicting studies. The studies have demonstrated the general safety of amiodarone with a low risk of proarrhythmia in such patients. Although side effects were present, they were not deemed life threatening and did not seem to increase mortality. The drug is safe in this group of patients and improves ventricular function (as observed in CHF-STAT) and decreases hospital admissions because of progressive congestive heart failure (as observed in GESICA). Based on these findings, amiodarone is the preferred drug to treat supraventricular arrhythmias in patients with congestive heart failure. The drug is effective in suppressing ventricular arrhythmias and therefore should be the drug of choice in patients with symptomatic ventricular arrhythmias associated with reduced ventricular function who require an antiarrhythmic drug. Both studies suggest that amiodarone may improve survival in patients with non-ischaemic heart disease and should be considered in such patients. Amiodarone cannot be recommended for use in patients with ischaemic cardiomyopathy and asymptomatic ventricular arrhythmias.

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